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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,163	09/26/2006	Kenichi Koyakumaru	701062	7239

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EXAMINER	
CLARK, SARA E	

ART UNIT	PAPER NUMBER
4121	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,163	KOYAKUMARU ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is a national stage (35 U.S.C. 371) application of PCT/JP05/06818, filed 3/31/2005, which claims benefit of priority to Japanese application 2004-108434, filed 3/31/2004. Claims 1-24, as amended, are pending.

Priority

1. Acknowledgment is made of applicant's claim to foreign priority under 35 U.S.C. 119(a)-(d). A proper claim was made on the ADS filed 9/26/2006 and the certified copy of Japanese application 2004-108434 has been received. Thus, claims 1-24 are entitled to an effective filing date of 3/31/2005, and a priority date of 3/31/2004.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 12/20/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

3. The disclosure is objected to because of the following informalities: the side chain hydroxyl group is identified throughout as the 21-hydroxyl group, although structural formulae I-VII show the hydroxyl group bonded to carbon 22. (see Moss, IUPAC Nomenclature of Steroids, p. 3). To avoid confusion, this Office Action refers to the side chain hydroxyl group as the 21-hydroxyl group, consistent with the specification and claims. However, appropriate correction is required.

Claim Objections

4. Claims 1-24 are objected to because of the following informalities: the side chain hydroxyl group is identified as the 21-hydroxyl group, although structural formulae I-VII show the hydroxyl group bonded to carbon 22 (see Moss, IUPAC Nomenclature of Steroids, p. 3). To avoid confusion, this Office Action refers to the side chain hydroxyl group as the 21-hydroxyl group, consistent with the specification and claims. However, appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakazawa et al. (US PG Pub. 2003/0180742, published 9/25/2003, supplied by Applicant on the IDS dated 12/20/2006) in view of Moriarty et al. (Tetrahed. Let. 35 (44) 8103-6, 1994).

Nakazawa et al. teach a method of producing 5α-pregnane derivatives as intermediates useful in squalamine synthesis, starting with (20S)-7α,21-dihydroxy-20-methyl-pregna-1,4-dien-3-one as a reactant (para. 20, "the diene") and resulting in

(20S)-7α,21-dihydroxy-20-methyl-5α-pregna-3-one as a product (para. 21, "the ketone").

Formula I-1 of Nakazawa et al. ((20S)-7α,21-dihydroxy-20-methyl-5α-pregna-1,4-dien-3-one, the unprotected diene, para. 20) is identical to formula I as recited in claims 1-24, where R2 is a hydrogen atom; it is noted that Nakazawa et al. do not teach a protecting group on the C21 hydroxyl (R1 of formula I).

Formula II-1 of Nakazawa et al. ((20S)-7α,21-dihydroxy-20-methyl-5α-pregna-3-one, the unprotected ketone, para. 21) is identical to formula VI as recited in claims 7-12, 14, 16, and 18-24; and identical to formula II where R11 and R12 are each independently a hydrogen atom, as recited in claims 1-6, 13, 15, and 17.

Formula III-1 of Nakazawa et al. ((20S)-7α,21-di-(O-protecting group)-20-methyl-5α-pregna-3-one, the protected ketone, para. 22) is identical to formula IV as recited in claims 7-12, 14, 16, and 18-24, where R21 and R22 are each a hydroxyl-protecting group.

The method of Nakazawa et al. teaches the steps of

(a) reducing the diene with lithium in the presence of ammonia (known as the Birch reduction) to reduce the double bonds at C1-C2 and C4-C5 to single bonds (paras. 12, 13, 50), in the presence of a proton donor such as ethanol (paras. 53, 72), as recited in claims 1-24; and

(b) protecting the C7 and C21 hydroxyl groups of the ketone with tert-butyl-dimethylsilyl protecting groups (paras. 14, 15, 42), as recited in claims 1-24.

Nakazawa et al. do not explicitly teach the "ene-one" of formula VII ((20S)-7α,21-dihydroxy-20-methyl-pregna-1-en-3-one; the unprotected ene-one); formula V ((20S)-7α-hydroxy-21-(O-protecting group)-20-methyl-pregna-1-en-3-one; the 21-protected ene-one), or formula III ((20S)-7α,21-dihydroxy-20-methyl-pregna-1-en-3-one, with neither, one, or both hydroxyl groups protected; i.e., formula VII, V, or (20S)-7α,21-di-(O-protecting group)-20-methyl-pregna-1-en-3-one (the 7,21-protected ene-one) of the instant claims, and therefore do not explicitly teach the production of a mixture of formulae II and III or a mixture of formulae VI and VII. However, formula III, where R11 and R12 are each independently a hydrogen atom, as recited in claims 1-6, 13, 15, and 17; and formula VII, as recited in claims 7-12, 14, 16, and 18-24, are inherently formed as intermediates during the course of the reduction step taught by Nakazawa et al. The reduction of the C4-C5 double bond proceeds faster than the reduction of the C1-C2 double bond (specification p. 4, lines 4-13), so as the diene is reduced, the process of Nakazawa et al. forms an intermediate mixture of the ketone and the ene-one (formulae II and III or VI and VII of the instant claims) until the reduction of the ene-one has gone to completion, even if it is not explicitly taught. The result is a uniform ketone product, which is the ultimate goal of the methods of both Nakazawa and the present invention (specification, Ref. Ex. 3). In summary, Nakazawa et al. explicitly teach formulae II, IV, and VI, and implicitly teach formulae III and VII.

While Nakazawa et al. teach all the steps, products, and reagents of the claimed invention, the reference does not teach the C21-protected intermediate of formula V as recited in claims 7-12, 14, 16, and 18-24, or the C21-protected reactant of formula I (i.e.,

where R1 is a hydroxyl-protecting group and R2 is hydrogen, the C21 hydroxyl group is protected and the 7α-hydroxyl is not), as recited in claims 2 and 8. This is because the method of Nakazawa et al. teaches the reduction and protection steps in the reverse order as recited in the claims, i.e., protecting the hydroxyl group(s) prior to the reduction step.

Moriarty et al. does teach hydroxyl-group protection prior to the reduction step as part of a multi-step synthesis of squalamine, in which the similarly reactive side chain hydroxyl group at C24 is protected with a tert-butyldimethylsilyl protecting group (step iv, yielding compound 4, pp. 8103-4), before the ene-one compound is subjected to the Birch reduction, using lithium in ammonia and ethanol (step vi, yielding compound 6 in 81% yield, p. 8104). Due to the reactivity of sterol side chain hydroxyl groups as compared to, for example, hydroxyl groups at C3 or C7, a result of steric effects, inductive effects, and other factors, the C24 hydroxyl protecting group of Moriarty et al. remains in place for most of the synthesis (twelve steps) before deprotection (step v, yielding compound 16, pp. 8104-5), recited as step (b) in claims 7-24. Further, Moriarty et al. teach the 7α-hydroxy group as unprotected for most of the synthesis following its introduction (nine steps) before a protecting group is added after deprotection of the C21 hydroxyl group. Thus, Moriarty et al. teach what Nakazawa does not, i.e., protecting the side chain hydroxyl group prior to the reduction step, while leaving the 7α-hydroxy group unprotected.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize (20S)-7α,21-dihydroxy-20-methyl-

5α-pregna-3-one using the same method and reagents taught by Nakazawa et al. but with the two steps reversed as taught by Moriarty et al., because, as recognized by MPEP 2144.04, selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1 and 2 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 13 of copending Application No. 10/,594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other because

- formula I recited in examined claims 1 and 2 is identical to formula I in reference claim 13, to include the scope of variable groups R1 and R2;
- formula II recited in examined claims 1 and 2 is identical to formula II in reference claim 13, to include the scope of variable groups R11 and R12;
- the process recited in examined claims 1 and 2 is identical to the process recited in reference claim 13, to include the production of a mixture of formulae II and III recited in examined claims 1 and 2, because
- formula III recited in examined claims 1 and 2, while not illustrated in reference claim 13, is necessarily formed as part of the process of reference claim 13, so that a mixture of compounds of formulae II and III is inherently produced by the process of reference claim 13.

In other words, examined claims 1 and 2 recite a reactant (formulae I), a process, and product (a mixture of formulae II and III) which are identical to the reactant, process, and products (formed as the reaction proceeds to completion) of reference claim 13.

9. Claims 3 and 4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 10/,594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other (a) for the reasons given in paragraph 8 above, and (b) in addition, the hydroxyl protecting species recited in reference claim 15 anticipates the genus recited in examined claim 3, and is identical to the species recited in examined claim 4.

10. Claims 5 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 7 of copending Application No. 10/,594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other (a) for the reasons given in paragraph 8 above, and (b) in addition, the metal species recited in reference claim 7 anticipates the genus recited in examined claim 5, and is identical to the species recited in examined claim 6.

11. Claims 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16 of copending Application No. 10/594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other because

- formula I recited in examined claims 7 and 8 is identical to formula I in reference claim 16, to include the scope of variable groups R1 and R2;

- formula VI recited in examined claims 7 and 8 is identical to formula IV in reference claim 16;
- formula IV recited in examined claims 7 and 8 is identical to formula III in reference claim 16, to include the scope of variable groups R21 and R22;
- the two-step process recited in examined claims 7 and 8 is identical to the process recited in reference claim 16, to include steps (a), (b), and the products formed:
    - a mixture of formulae IV and V as recited in examined claims 7 and 8, because formula V, while not illustrated in reference claim 16, is necessarily formed as part of the process of reference claim 16, so that a mixture of compounds of formulae IV and V is inherently produced by the process of reference claim 16; and
    - a mixture of formulae VI and VII recited in examined claims 7 and 8, because formula VII, while not illustrated in reference claim 16, is necessarily formed as part of the process of reference claim 16, so that after step (b), deprotection, a mixture of compounds of formulae VI and VII is inherently produced by the process of reference claim 16.

In other words, examined claims 7 and 8 recite a reactant (formulae I), a process having two steps, a protected first product (a mixture of formulae IV and V), and a deprotected second product (a mixture of formulae VI and VII) which are identical to the reactant, process, and products (formed as the reaction proceeds to completion) of reference claim 16.

12. Claims 9 and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 10/,594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other (a) for the reasons given in paragraph 11 above, and (b) in addition, the hydroxyl protecting species recited in reference claim 18 anticipates the genus recited in examined claim 9, and is identical to the species recited in examined claim 10.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1, 7, and 11-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 13-18 of copending Application No. 10/594,164 in view of Nakazawa et al. and Moriarty et al., as cited above.

The metal subgenus recited in examined claims 11, 13, 15, 17, 19, 21, and 23 (alkali metal) and the species recited in examined claims 12, 14, 16, 18, 20, 22, and 24 (lithium) fall within the scope of reference claims 8, 13, 14, 15, 16, 17, and 18, respectively, which recite the genus alkali metals and alkaline earth metals. However, claims 6 and 7 of copending Application No. 10/,594,164 recite the subgenus alkali metals and the species lithium, respectively; and the definition of alkali metals and alkaline earth metals in the specification notes that "[o]f these, alkali metals such as lithium, sodium, potassium, and the like are preferable, and lithium is more preferable" (p. 13). In addition, the methods of both Nakazawa et al. (para. 8) and Moriarty et al. (p.

8104) teach the use of lithium as the alkali metal to be used in the Birch reduction step. Therefore, in addition to the reasons given in paragraphs 8 and 11, it would have been obvious to one of ordinary skill in the art at the time the invention was made to specifically choose lithium as the alkali or alkaline earth metal as the reducing agent in the method of the examined claims.

This is a provisional obviousness-type double patenting rejection.

Conclusion

14. Claims 1-24 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEC

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121